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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,098	04/11/2001	Randal J. Kaufman	UMV-1184CPCN	4065
959	7590	10/23/2003	EXAMINER	
LAHIVE & COCKFIELD 28 STATE STREET BOSTON, MA 02109			DESAI, ANAND U	
			ART UNIT	PAPER NUMBER
			1653	

DATE MAILED: 10/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/819,098	KAUFMAN ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Anand U Desai	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 16 October 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 5-7, 9, 12 and 14-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 8, 10, 11 and 13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                  | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>1</u> . | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election without traverse of Group I, Claims 1-4, 8, 10, 11, and 13 filed August 11, 2003 is acknowledged. Claims 5-7, 9, 12, and 14-16 have been withdrawn from further consideration by the Examiner because these claims are drawn to non-elected inventions. Claims 17-40 are cancelled without prejudice. Claims 1-4, 8, 10, 11, and 13 are currently under examination.

### ***Priority***

2. Priority to U.S. Patent Application 08/980038 filed November 26, 1997 which claims benefit of priority to PCT/US97/06563 filed April 24, 1997 which claims benefit of priority to provisional application 60/016,117 filed April 24, 1996 and 60/017,785 filed May 15, 1996 is acknowledged.

### ***Specification***

3. The disclosure is objected to because of the following informalities: There is a typographical error on page 15, line 34, where "Plasmid c nstruction" appears to be Plasmid construction.

The application claims a modified Factor VIII polypeptide, but no sequence information has been submitted. Applicant is referred to MPEP Rules 1.821-1.825 in reference to amino acid sequence disclosure in a patent application.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-4, 8, 10, 11, and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Is procoagulant-active FVIII a pro-FVIII protein (similar to a prohormone) or is it FVIII protein that is activated by thrombin?

***Claim Rejections - 35 USC § 102***

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1-4, and 8 are rejected under 35 U.S.C. 102(a) as being anticipated by Marquette et al. (The Journal of Biological Chemistry, Vol 270, No. 17, pp. 10297-10303 April 28 (1995)). Marquette et al. teaches a procoagulant human Factor VIII protein that is modified at phenylalanine located at position 309 (See 5<sup>th</sup> paragraph in Experimental Procedures, page 10298, the generation of chimeric factor VIII protein with the A1 domain of factor V (amino acids 198-312) replacing the A1 domain of factor VIII (amino acids 226-335); **Claim 1**). The mutations taught are both a substitution (see above reference location; **Claim 2**) and a deletion mutation (See 4<sup>th</sup> paragraph in Experimental Procedures, page 10298, the generation of Factor VIII deletion removes amino acids 226-371; **Claim 3**). The substituted mutation changes the

phenylalanine at 309 with a serine residue (see above reference location and figure 5 on page 10302; **Claim 4**). The Factor VIII protein was administered in a clotting assay as a pharmaceutical composition 10<sup>th</sup> paragraph in Experimental Procedures, page 10299; **Claim 8**).

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 10 and 13 are rejected under 35 U.S.C. 103(a) as being obvious over Pittman et al. (Proc. Natl. Acad. Sci., Vol. 85, pp. 2429-2433 (1988) in view of Kaufman et al. U.S. Patent 5,451,521 (Effective filing date= December 9, 1986). Pittman et al. teaches an Arginine to Isoleucine mutation at position 336 for Factor VIII protein. There is an increase in coagulation activity of the Factor VIII variant compared to wild type Factor VIII, and the variant Factor VIII was resistant to inactivation due to cleavage by either thrombin, Factor Xa, or Activated Protein C (APC) (6<sup>th</sup> paragraph in Results section, pg 2432, and 2<sup>nd</sup> paragraph in Discussion section, pg

2433). Pittman et al. does not teach the Arginine to Lysine mutation at position 562, although there is motivation to suggest other inactivation cleavage sites (2<sup>nd</sup> paragraph in Discussion section, pg 2433). Kaufman et al. teaches Factor VIII variants that have changes in amino acids at cleavage sites, 336, and 562 that maybe conservative changes or alternatively non-conservative changes, such as Arg to Lys and Arg to Ile (column 2, lines 46-61 and claim 1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to make an inactivation resistant human Factor VIII protein with mutations at position 336 and 562 (**Claim 10**). Kaufman et al. also teaches a pharmaceutical composition comprising an effective amount of the modified Factor VIII polypeptide (claim 25; **Claim 13**).

11. Claim 11 is rejected under 35 U.S.C. 103(a) as being obvious over Marquette et al. (The Journal of Biological Chemistry Vol, 270, No. 17, pp. 10297-10303 April 28 (1995)) in view of Kaufman et al. (U.S. Patent 5,451,521, Effective filing date=December 9, 1986). Marquette et al. teaches a procoagulant human Factor VIII protein that is modified at phenylalanine located at position 309 (See 5<sup>th</sup> paragraph in Experimental Procedures, page 10298, the generation of chimeric factor VIII protein with the A1 domain of factor V (amino acids 198-312) replacing the A1 domain of factor VIII (amino acids 226-335) that has improved secretion. Kaufman et al. teaches human Factor VIII protein that has modifications at Arginine 336 and 562. The modifications taught are conservative such as lysine at 562 and non-conservative such as isoleucine at 336 (column 2, lines 46-61). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to make an inactivation resistant human Factor VIII protein with improved secretion (**Claim 11**).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U Desai whose telephone number is (703) 305-4443. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 4:30 p.m..


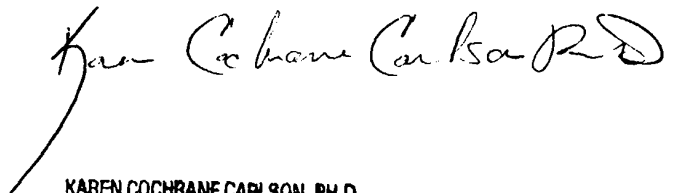
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Art Unit: 1653

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.

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October 16, 2003

A handwritten signature in black ink, appearing to be "J. D. ...".A handwritten signature in black ink that reads "Karen Cochrane Carlson PhD".

KAREN COCHRANE CARLSON, PH.D  
PRIMARY EXAMINER